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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SCHLIENTZ, LEAH H	

ART UNIT	PAPER NUMBER
1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/826,690	LEGRAND ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,9,10,13-15,17-22 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9,10,13-15,17-22 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement of Receipt

Applicant's Response, filed 7/30/2010, in reply to the Office Action mailed 4/30/2010, is acknowledged and has been entered. Claims 1, 4-6, 9, 10, 13, 17-19 and 22 have been amended. Claims 1-6, 9, 10, 13-15, 17-22 and 24 are pending and are examined herein on the merits for patentability.

Response to Arguments

Any rejection not reiterated herein has been withdrawn.

Applicant's arguments have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of newly discovered prior art references.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-6, 9, 13-15, 17, 20, 22 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li *et al.* (US 2003/0035840), as evidenced by Sigma-Aldrich Particle Size Conversion.

Li teaches a delayed, sustained release pharmaceutical preparation which provides longer delay of drug dissolution thereby allowing greater flexibility in designing sustained release profiles, providing improved plasma levels wherein maximum plasma concentration can be substantially reduced without a concomitant reduction in AUC (paragraph 0019). The invention involves a pelletization process typified by application of a bupropion/cellulose ether suspension to inert spheres and two unique formulations which are applied to separate active drug pellets. The formulation functions by membrane-controlled extended release in a pH dependent manner (paragraph 0027). Less than 50% of the drug is released at ten hours (paragraph 0029). The core forming inert component may comprise any type of commonly known pellet starting material such as starch or sugar spheres having a diameter which is preferably 30 to 35 mesh (paragraph 0054). The inert core is preferably coated with an aminoketone antidepressant agent, preferably bupropion (paragraph 0055) and a binding agent such as HPMC (paragraph 0056-0057). The active pellets are divided into two groups each group receiving a film coating which releases the drug at a different pH. One group of pellets is film coated to release drug at a pH corresponding to pH 4.8 and lower which

is likely to occur in the upper GI tract; the other group of pellets is film coated to release drug at a pH of 7 and above which is likely to occur in the lower GI tract (paragraph 0060). The first group of pellets is film-coated with a film comprising a pH dependent coating polymer, a plasticizer and a lubricant. The pH dependent coating polymer is selected from enteric coating polymers known in the art such as methacrylic acid copolymers, hydroxypropyl methylcellulose phthalate (HPMCP) (i.e. corresponding to polymer A in the instant claims); preferably in a concentration of 2-10%, preferably 3-5% of the total dosage form (paragraph 0061-0062). The coating includes a lubricant such as glyceryl monostearate, myvaplex 600P (i.e. corresponding to compound B in the instant claims), which is present in an amount of 1-15%, preferably 1-2.5%. The coating which comprises one third of the capsule content is preferably comprised of the following ingredients, shown in paragraphs 0064-0065.

INGREDIENT	PREFERRED	MOST PREFERRED
HPMCP	2–10%	3–5%
Acetyltributyl citrate	0.1–3%	0.5–1%
Glyceryl monostearate	1–3%	1–2.5%

See also Example 1, showing active core pellets having a film coating comprising the following amounts:

bupropion active pellets	75%
HPMCP 50	16.9%
acetyltributyl citrate	2.5%
myvaplex 600P	5.6%

Release profiles for capsules comprising the pellets are shown at pH 7.5 and pH 1.5 in Figures 1 and 2. The two groups of pellets are blended together to obtain a

finished product and are placed in a gelatin capsule. Alternatively, they may be made into tablets (paragraph 0072).

Sigma-Aldrich Particle Size Conversion is included to show that sugar spheres having a diameter of the preferred 30-35 mesh corresponds to 500-595 micron particle size.

It would have been obvious to one of ordinary skill in the art at the time of the invention to provide active pellets of the claimed diameter with a coating comprising a pH dependent coating polymer, such as methacrylic acid copolymers or hydroxypropyl methylcellulose phthalate in the range of 3-5% and a lubricant such as glyceryl monostearate in the range of 1-2.5%. It is noted that the pellet formulation in Example 1 shows a ratio of 5.6% compound B (glycerol monostearate) to 16.9% polymer A (HPMCP), or a 0.33 : 1 weight ratio of B/A, which is less than the 0.5 – 1.5 ratio claimed. However, the preparation of pharmaceutical compositions having various amounts of the formulation components is within the level of skill of one having ordinary skill in the art at the time of the invention. One of ordinary skill could have readily modified the concentration of pH dependent polymer and lubricant as a matter of routine experimentation, and would have been motivated to do so in order to determine optimal performance of coated pellets, such as by selection of amounts from the preferable ranges of coating components taught by Li, which are overlapping with the claimed ratio. For example, selection of 2.5% glycerol monostearate from the preferred range shown above, and varying HPMCP in any amount of the preferred range of 3.5-5% would be well within the claimed ratio of A/B. Furthermore, differences in concentration

or temperature will generally not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." See *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); *In re Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382; or *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969).

Regarding the claimed release profile, the composition as a whole taught by Li appears to release without lag phase at ph 7.5 shown in Figure 1, and the composition as a whole appears to release at least some drug at 4-5 hours in pH 1.5, which is interpreted to be substantially overlaping with the claimed release profile having a latency phase with a duration of less than or equal to 5 hours at pH 1.4. It is noted that the comprising language of the instant claims does not exclude the presence of additional pellets in the formulation.

Regarding claim 3, the amount of coating in Example 1 corresponds to 25% of the weight of the pellets.

Regarding claims 14 and 15, 50% of drug is released at ten hours.

Claims 1-6, 9, 13-15, 17, 20-22 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li *et al.* (US 2003/0035840), as evidenced by Sigma-Aldrich Particle Size Conversion, in view of Dante (US 6,034,091).

The rejection over Li is applied as above.

Li does teaches formulation of bupropion, rather than fluoxetine as an anti-depressant.

Dante teaches that a-typical antidepressants include but are not limited to bupropion, sertraline, fluoxetine and trazodone and their pharmacologically effeictive salts and ester (column 1-2).

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute one known a-typical antidepressant for another in the formulation taught by Li, such as substitution of fluoxetine for bupropion. One would have been motivated to do so in order to provide functionally equivalent anti-depressant drugs having an expected delayed, sustained release profile.

Claims 1-6, 9, 13-15, 17-20, 22 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li *et al.* (US 2003/0035840), as evidenced by Sigma-Aldrich Particle Size Conversion, in view of Ishibashi (EP 1101490).

The rejection over Li is applied as above.

Li teaches that any commonly known pellet starting material such as starch or sugar spheres having a diameter ranging from 15 to 50 mesh, preferably 30 to 35 mesh may be used, but does not specifically recite lactose of cellulose microspheres.

Ishibashi teaches examples of inert carriers include cyrstallines of sugars or inorganic salts such as crystalline of lactose, microcrystalline cellulose, spherical granulated material (such as the spherical granulated material of crystalline cellulose, etc.).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use lactose or cellulose microspheres as the neutral core in the formulation taught by Li. One would have been motivated to do so and would have had a reasonable expectation of success in doing so because Li teaches that any commonly known pellet starting material such as starch or sugar spheres may be used, and Ishibashi teaches that lactose and microcelluose microspheres are well known in the art to be useful neutral cores for preparing microcapsules.

Claims 1-6, 9, 10, 13-15, 17, 20, 22 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li *et al.* (US 2003/0035840), as evidenced by Sigma-Aldrich Particle Size Conversion, in view of Seth (US 6,096,341).

The rejection over Li is applied as above.

Li teaches that suitable lubricants include glyceryl Monostearate, myvaplex 600P, calcium stearate or stearic acid, but does not specifically recite glyeryl behenate as lubricant.

Seth teaches preparation of controlled release tablets of bupropion hydrochloride (abstract). Examples of lubricants include stearic acid, magnesium stearate, glyceryl behenate, etc. (column 2, lines 5-10).

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute glyeryl behenate as a functionally equivalent lubricant to stearic acid, glycerol monostearate, etc. in the delayed, sustained release formulations of bupropion taught by Li. The Supreme Court in KSR International Co. v. Teleflex Inc.,

550 U.S. ___, 82 USPQ2d 1385, 1395-97 (2007) identified a number of rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as laid down in Graham. One such rationale includes the simple substitution of one known element for another to obtain predictable results. The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. See MPEP 2143. In the instant case, the substituted components (glyceryl behenate, stearic acid, glycerol monostearate) and their functions were known in the art at the time of the instant invention. For example, Li teaches that suitable lubricants include stearic acid, glycerol monostearate. Seth teaches that lubricants include stearic acid, magnesium stearate, glyceryl behenate, etc. (column 2, lines 5-10). One of ordinary skill in the art could have substituted one known lubricant for another, and the results of the substitution would have been predictable, that is formulation of a delayed, sustained release microparticulate dosage form having pellets having a coating comprising a pH dependent polymer and a lubricant.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is (571)272-9928. The examiner can normally be reached on Monday-Tuesday and Thursday-Friday 9 AM-5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS